A practical overview of the treatment of chronic hepatitis C virus infection

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Background

Although hepatitis C virus (HCV) infection is associated with significant morbidity and mortality, <2% of affected individuals in Australia receive treatment. New direct-acting antiviral (DAA) therapies are now available on the Pharmaceutical Benefits Scheme (PBS), and can be prescribed by any general practitioner (GP) in consultation with an experienced specialist.

Objective

This article provides an overview for GPs on the principles involved in assessing and treating patients with chronic hepatitis C within a community setting.

Discussion

Treatment with DAA medications listed on the PBS should be considered for all patients with chronic HCV infection. These regimens are well tolerated, highly efficacious and have all-oral administration. A thorough pre-treatment evaluation should be undertaken, and patients with cirrhosis, significant comorbidities or potential drug–drug interactions should be referred to a specialist. Successful eradication of HCV is characterised by undetectable HCV ribonucleic acid viral load on polymerase chain reaction testing 12 weeks after treatment completion, although antibodies to HCV may remain positive for the rest of the patient's life.

Affecting more than 230,000 individuals in Australia, hepatitis C virus (HCV) infection is a common cause of chronic liver disease, leading in many cases to cirrhosis, decompensated disease, liver cancer and death.[1,2] Despite significant morbidity and mortality, it is estimated that <2% of people with chronic HCV infection receive treatment.[3,4] A key contributor to this low treatment uptake has been a lack of infrastructure available to administer therapy, which was previously undertaken only through specialist liver disease clinics or via specially trained and accredited GPs.[5]

As of March 2016, new oral direct-acting antiviral (DAA) treatments for HCV became available on the Pharmaceutical Benefits Scheme (PBS) for patients >18 years of age in Australia. These treatments can be prescribed by GPs in consultation with a gastroenterologist, hepatologist or infectious diseases physician experienced in the treatment of chronic HCV infection.[6]

Logistically, the nature of this consultation varies in different states and territories; however, most patients with uncomplicated HCV infection can be treated in the community without being seen by a specialist. The nationally standardised *Remote consultation request for initiation of hepatitis C treatment form* from the Gastroenterological Society of Australia (available at www.gesa.org.au/professional.asp?cid=77&id=454) is an easily accessible document that can be submitted to many treatment centres in Australia for sighting and approval by an appropriate physician.

Implementation of the new treatment paradigm has far-reaching implications, as the vast majority of patients with chronic HCV infection have not been referred to specialty services or considered for treatment.[7] Empowering primary care physicians to facilitate rapid work-up and treatment of the disease allows treatment to be offered in the community to individuals who are unable to readily access specialty services.

The purpose of this article is to provide a practical overview of the approach to and treatment of HCV infection within the community setting for primary care physicians.

Pre-treatment evaluation

The new DAA medications are associated with average cure rates of >90%. They are better tolerated, are orally administered and are more effective than previous therapies for HCV infection.[8] As such, everyone living with chronic HCV infection should be considered for antiviral treatment, even if they have tried and failed interferon-based therapy in the past.

Prior to commencing DAA therapy, patients should undergo a thorough pre-treatment evaluation (Box 1). This should include identifying the genotype of hepatitis C involved, whether there is evidence of cirrhosis, and if treatment had been previously attempted. These factors directly influence the choice and

Box 1. Core concepts in the pre-treatment evaluation of patients with HCV infection

Is the patient infected with HCV? If so, what is the genotype?

- HCV antibody positive indicates exposure
- HCV viral load (PCR) indicates current infection
- Hepatitis C genotype

Is there evidence of cirrhosis?

- Physical examination: spider naevi, palmar erythema, gynaecomastia, splenomegaly
- Biochemical tests: thrombocytopenia, low albumin, prolonged PT/ INR, aspartate aminotransferase-to-platelet ratio index >1.0
- Imaging: ultrasonography or elastography (FibroScan)

Is the patient treatment-naive or treatment-experienced?

Do other medical conditions need optimisation first?

- Patient has significant comorbidities or concurrent infections
- Patient has prominent psychiatric issues that may interfere with medication compliance
- Patient will soon be undergoing surgery that may make administration of medications more challenging

Do medication interactions need to be addressed?

- Some antiepileptics, such as carbamazepine and phenytoin, are contraindicated, whereas others, such as sodium valproate and levetiracetam, are safe
- Proton pump inhibitors may need to be taken at reduced doses and with the same administration time as certain antivirals (eg ledipasvir + sofosbuvir)

Does the patient need to be referred to a specialist for treatment?

- Patients with cirrhosis, significant comorbidities or challenging drug–drug interactions should be referred

HCV, hepatitis C virus; INR, international normalised ratio; PCR, polymerase chain reaction; PT, prothrombin time

Table 1. Examples* of approved regimens for HCV under the Pharmaceutical Benefits Scheme[6]

		Genotype 1	Genotype 2	Genotype 3	Genotypes 4–6
Non-cirrhotic	Treatment-naive	Ledipasvir + sofosbuvir (8 or 12 weeks†)	Sofosbuvir + ribavirin (12 weeks)	Daclatasvir + sofosbuvir (12 weeks)	Sofosbuvir + PEG-IFN + ribavirin (12 weeks)
	Treatment-experienced	Ledipasvir + sofosbuvir (12 weeks)	Sofosbuvir + ribavirin (12 weeks)	Daclatasvir + sofosbuvir (12 weeks)	Sofosbuvir + PEG-IFN + ribavirin (12 weeks)
Cirrhotic	Treatment-naive	Ledipasvir + sofosbuvir (12 weeks)	Sofosbuvir + ribavirin (12 weeks)	Daclatasvir + sofosbuvir (24 weeks)	Sofosbuvir + PEG-IFN + ribavirin (12 weeks)
	Treatment-experienced	Ledipasvir + sofosbuvir (24 weeks)	Sofosbuvir + ribavirin (12 weeks)	Daclatasvir + sofosbuvir (24 weeks)	Sofosbuvir + PEG-IFN + ribavirin (12 weeks)

**A full list of approved regimens is available at www.pbs.gov.au/info/healthpro/explanatory-notes/general-statement-hep-c*
†Treatment for 8 weeks can be considered if pre-treatment HCV viral load is <6 million IU/mL
HCV, hepatitis C virus; PEG-IFN, peginterferon alfa-2a

duration of therapy. As compliance is a key component of treatment success, comorbid physical or psychological conditions should also be optimised before commencing therapy.

Several groups of patients will require referral to a specialist for treatment, particularly those with current or prior evidence of decompensated cirrhosis, such as encephalopathy, previous variceal bleeding or refractory ascites.[4] Regardless of the degree of compensation, individuals with cirrhosis will benefit from specialist review to assess readiness to commence therapy and assist with other aspects of care (eg variceal surveillance, hepatocellular carcinoma screening).

In cases where a diagnosis of cirrhosis is uncertain, referral for elastography (FibroScan) is the authors' preferred method for establishing the degree of fibrosis. Thrombocytopenia, prolonged prothrombin time (PT)/ international normalised ratio (INR) and hypoalbuminaemia are biochemical features that suggest the presence of cirrhosis. In the absence of elastography, a variety of other non-invasive tools, such as the aspartate aminotransferase-to-platelet ratio index (APRI) or Hepascore, can assist in establishing a diagnosis.[9]

Other patient groups that warrant closer specialist input are those in whom multiple comorbidities or concomitant medications make choosing the right regimen challenging. Many DAAs and their metabolites are renally cleared, and as such, their dosing in those with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2) can be challenging. Other key considerations before commencing therapy are potential drug–drug interactions. Discontinuation of, or alternatives to, certain medications such as macrolide antibiotics, St John's wort and certain antiepileptics, such as carbamazepine or phenytoin, is critical. The University of Liverpool drug–drug interaction checker (available online at www.hep-druginteractions.org) is a useful tool for ensuring there are no relevant drug–drug interactions.

Treatment

Six genotypes of hepatitis C have been identified, although genotypes 1 and 3 comprise 90% of all cases in Australia.[10] An example of an approved treatment regimen for each genotype is listed in Table 1. Most of these regimens consist of once daily dosing; side effects of fatigue, headache, nausea and insomnia are uncommon and typically mild, and rarely necessitated cessation of the drug in clinical trials.[11] In contrast to traditional interferon-based treatment regimes, intensive monitoring during therapy with DAAs is therefore seldom required. Nonetheless, it should be emphasised to patients that poor adherence to the daily dosing regimen can significantly affect response to therapy.

Treatment response is assessed 12 weeks after completion of therapy, with an assessment of hepatitis C viral load by polymerase chain reaction (PCR). Successful treatment is characterised by an undetectable level indicative of sustained virologic response (SVR). Although patients will remain positive for HCV antibodies, those who achieve SVR at 12 weeks should no longer be considered as being infected with the virus.[12,13] However, it should be noted that positive serology is not a marker of protection, and repeat exposure may lead to re-infection.

Treatment of HCV is also an effective therapy for extrahepatic manifestations of hepatitis C such as cryoglobulinaemia and glomerulonephritis, and these should also demonstrate lasting improvement following treatment.[11]

Patients with normal liver function tests after SVR can be managed as if they had never been infected with HCV; however, high-risk behaviours should be addressed if present. Individuals with ongoing liver function test derangement, or those who have failed to achieve SVR, maintain a requirement for entry into surveillance programs and specialist involvement to pursue further therapeutic options.

Conclusion

Treatment of HCV infection should be considered for everyone in Australia who has a chronic infection. The relative scarcity of specialist services, compared with the prevalence of the disease, clearly suggests that treatment cannot be managed by specialists alone. Australia's new model of care provides primary care physicians with streamlined access to highly effective and well-tolerated oral DAA therapy in consultation with experienced specialists. Furthermore, non-cirrhotic individuals with no significant comorbidities, concurrent infections or relevant drug–drug interactions rarely need to see these specialists in person to complete treatment.

Cure of chronic HCV infection has the potential to significantly improve the health of 230,000 Australians, decrease mortality from complications of chronic infection and reduce the burden of liver disease in Australia's healthcare system.

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